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EXAMINER	
ROYDS, LESLIE A	
ART UNIT	**PAPER NUMBER**
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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/631,106	BROWN, DENNIS M.	
	Examiner	Art Unit	
	Leslie A. Royds	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 15-25 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 15-25 is/are rejected.

7)☒ Claim(s) 15 is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date 19 July 2005.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claims 15-25 are presented for examination.

Acknowledgment is made of the present application as a divisional application of U.S. Patent Application No. 09/834,177, filed April 12, 2001, now U.S. Patent No. 6,630,173, which claims benefit under 35 U.S.C. 119(e) to U.S. Provisional Patent Application No. 60/197,103, filed April 12, 2000. Acknowledgement is also made of the present application as a continuation-in-part (CIP) application of U.S. Patent Application No. 09/810,527, filed March 15, 2001, now U.S. Patent No. 6,734,178. Applicant's preliminary amendment filed July 31, 2003 has been received and entered into the application. Accordingly, claims 1-14 are cancelled and claims 15-25 are newly added. Applicant's Information Disclosure Statement (IDS) filed July 19, 2005 has also been received and entered into the application. As reflected by the attached, completed copy of form PTO/SB/08A (two pages total), the Examiner has considered the cited references, except those references designated as C2-C9 and C11 at page 1 of the IDS and those references designated as C12, C16-C18 and C24 at page 2 of the IDS. Such references could not be located in the parent applications after a reasonable search and, thus, have not been considered.

Applicant's Claim for Priority under 35 U.S.C. 119(a-d) and 120

Applicant's claim for the benefit of a domestic-filed application (U.S. Patent Application Nos. 09/834,177 and 09/810,527) under 35 U.S.C. 120 and Applicant's claim for the benefit of a provisional application (U.S. Provisional Patent Application No. 60/197,103) under 35 U.S.C. 119(e) is acknowledged. Applicant is reminded that the later-filed application must be an

application for patent for an invention that has been disclosed in the prior parent applications. The disclosure of the invention in the earlier application(s) and in the later-filed application must be sufficient to comply with the requirements of the first paragraph of 35 U.S.C. 112. See *Transco Products, Inc. v. Performance Contracting, Inc.*, 38 F.3d 551, 32 USPQ2d 1077 (Fed. Cir. 1994).

It has been determined that U.S. Patent Application No. 09/810,527, filed March 15, 2001, contains sufficient support and enablement as required under 35 U.S.C. 112, first paragraph, for the presently claimed subject matter drawn to a combination of amonafide and homoharringtonine for the treatment of a host with a cellular proliferative disease. In light of this fact, the effective filing date of present claims 15-25 has been determined to be March 15, 2001.

Objection to the Claims

Claim 15 is objected to for reciting, "comprising an amonafide", which is grammatically awkward. Amonafide itself it a discrete chemical entity and does not require the indefinite article "an" to precede it in the claim. Appropriate correction is required.

Objections to the Specification

Applicant's preliminary amendment amending the present specification at page 1, directly following the title, has been noted in the papers filed July 31, 2003. It is noted that Applicant has not provided the current status of each of the applications to which it claims priority. Applicant is requested to amend the cross-reference to these related applications to

properly reflect the current status of the application.

Applicant may wish to consider amending page 1, directly following the title, in the following manner. Applicant is reminded that the following is a suggestion and the adoption of such a suggestion does not necessarily equate to the claims being free of the cited prior art.

---This application is a division of United States Application Serial No. 09/834,177, filed April 12, 2001, now U.S. Patent No. 6,630,173, which claims the benefit of United States provisional application Serial No. 60/197,103, filed April 12, 2000. This application is also a Continuation-in-Part of United States Application Serial No. 09/810,527, filed March 15, 2001, now U.S. Patent No. 6,734,178.---

The disclosure is objected to because the paragraph at lines 17-31 of page 4 fails to conclude with a period.

Claim Rejection - 35 USC § 112, Written Description and Enablement

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Written Description Requirement

Claims 15-24 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims contain subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

An Applicant shows possession of the claimed invention by describing the claimed invention with all of its limitations using such descriptive means as words, structures, figures, diagrams and formula that fully set forth the claimed invention. *Lockwood v. American Airlines, Inc.*, 41 USPQ2d 1961, 1966 (Fed. Cir. 1997).

The present rejection is made in accordance with the MPEP at §2163, which states, "The issue of a lack of adequate written description may arise even for an original claim when an aspect of the claimed invention has not been described with sufficient particularity such that one skilled in the art would recognize that the Applicant had possession of the claimed invention."

In particular, the specification as originally filed fails to provide sufficient written description for treating the genus of disorders known in the art as cellular proliferative diseases, nor does it provide sufficient written description for employing any naphthalimide agent in conjunction with any antiproliferative agent in the presently claimed method. While Applicant has provided sufficient written description for the use of the naphthalimide compound amonafide in conjunction with the antiproliferative agents cisplatin (see Example 1 and Table 5, Groups 14-15), paclitaxel (see Table 5, Group 16), vinblastine (see Table 5, Group 17), etoposide (see Table 5, Group 18), 5-fluorouracil (see Table 5, Group 19), homoharringtonine (see Table 5, Group 21), colchicines (see Table 5, Group 22), curcumin (see Table 5, Group 23) and parthenolide (see Table 5, Group 24), for the treatment of fibrosarcoma, Applicant has failed to provide sufficient evidence demonstrating that he was in possession of the concept of using all known naphthalimide compounds in combination with all known antiproliferative agents for treating a host with any known cellular proliferative disease.

Present claim 15 is drawn to a method for treating a host with a cellular proliferative disease comprising the administration to said host a naphthalimide comprising amonafide in conjunction with an antiproliferative agent comprising homoharringtonine, each in an amount sufficient to modulate said cellular proliferative disease. However, it is noted that the claims are not definitively limited solely to the administration of amonafide in combination with homoharringtonine. In fact, the recitation of the broader limitations "naphthalimide" and "antiproliferative agent" and the exemplary nature of the limitations "amonafide" and "homoharringtonine" renders the scope of the claim readable on any naphthalimide compound known in the art and any antiproliferative agent known in the art.

Considering the breadth of compounds encompassed by the limitation "naphthalimide" or "antiproliferative agent" and the breadth of diseases encompassed by the limitation "cellular proliferative disease" that are appreciably disparate in etiology and pathophysiological manifestations, the mere disclosure and exemplification of amonafide as a naphthalimide compound, cisplatin, paclitaxel, vinblastine, etoposide, 5-fluorouracil, homoharringtonine, colchicine, curcumin and parthenolide as antiproliferative agents and fibrosarcoma as a cellular proliferative disease is not adequate written description of a representative number of species of agents encompassed by the large and varied genera of "naphthalimide" or "antiproliferative agent" that would be amenable to combination such that they would have efficacy in treating a cellular proliferative disease, nor is it adequate written description of a representative number of species of disease encompassed by the large and varied genus of "cellular proliferative disease" that would be amenable to treatment with such a combination of agents.

First, the sheer number of compounds that are considered naphthalmides or antiproliferative agents is so vast that the mere representation of amonafide or cisplatin, paclitaxel, vinblastine, etoposide, 5-fluorouracil, homoharringtonine, colchicine, curcumin and parthenolide, respectively, is most certainly not representative of the entire genus of agents that are encompassed by the broad limitation "naphthalimide" or "antiproliferative agent" that could be used in conjunction with the reasonable expectation that it would have had therapeutic activity in treating a cellular proliferative disease. In fact, the full scope of compounds that fall within the scope of these broad genera are appreciably dissimilar from one another in chemical structure, function and physical properties such that the activity of the agents exemplified in the present disclosure could not be reasonably extrapolated to each and every naphthalimide compound or antiproliferative agent that is known in the art. Notwithstanding that Applicant has disclosed a common core naphthalimide structure, the exemplification of one single naphthalimide agent is, respectfully, not sufficient to then claim the entire genus of compounds known to share such a naphthalimide structure in the absence of any scientific reasoning as to why the results demonstrated with amonafide would have been predictive of the same or substantially similar results using any other naphthalimide compound known in the art.

Regarding the genus of "antiproliferative agents", Applicant has failed to disclose any relevant, identifying characteristics, such as structure or other physical or chemical properties, or other functional characteristics, that would have been sufficient to show that Applicant was in possession of the claimed genus of antiproliferative agents, in general. See *Eli Lilly*, 119F.3d at 1568, 43 USPQ2d at 1406. See also MPEP §2163.

The same reasoning applies to the genus of "cellular proliferative disease". While Applicant may have demonstrated the efficacy of amonafide in combination with a selection of antiproliferative agents (i.e., cisplatin, paclitaxel, vinblastine, etoposide, 5-fluorouracil, homoharringtonine, colchicine, curcumin and parthenolide) in treating fibrosarcoma, it remains that the genus of cellular proliferative diseases is highly varied and encompasses a considerable number of diseases that are sufficiently dissimilar in etiology, pathophysiological manifestations and treatment regimens such that the exemplification of one disease (i.e., fibrosarcoma) could not be reasonably extrapolated to each and every one cellular proliferative disease that is known in the art. For example, psoriasis is distinctly different than cancer in terms of the agents used, frequency of treatment, route of administration, dosage amounts, etiology and pathophysiological manifestations such that the activity of a composition in treating psoriasis would not have necessarily been reasonably suggestive of the same or substantially similar activity in any one or more other cellular proliferative diseases. Furthermore, given the disparate and distinct nature of all known cancers, the mere exemplification of fibrosarcoma is most certainly not a representative showing of species to then claim the treatment of the entire genus of "solid tumors". The high degree of complexity in cancer treatment and the appreciable differences in etiology and pathophysiology of different cancer types would have necessarily cast significant doubt on whether the presently claimed combination of agents would have exerted the same therapeutic effect in any known solid tumor.

Applicant has failed to provide any sound scientific reasoning as to why the data shown in the present specification for the combination of amonafide with cisplatin, paclitaxel, vinblastine, etoposide, 5-fluorouracil, homoharringtonine, colchicine, curcumin and parthenolide

in murine fibrosarcoma cells is a showing of results of a representative number of species encompassed by the limitations "naphthalimide", "antiproliferative agent" or "cellular proliferative disease" and how such results could be extrapolated out to the genus of naphthalimides in general, antiproliferative agents in general or cellular proliferative diseases in general with the realistic expectation that the same or substantially similar efficacy in achieving the presently claimed therapeutic effect could have been reasonably guaranteed.

Considering the teachings provided in the specification as originally filed, Applicant has failed to provide the necessary teachings, disclosure or reasoning to fully set forth the claimed invention in such a way as to reasonably convey to one skilled in the relevant art that Applicant had possession of the entire genus of naphthalimides, antiproliferative agents and cellular proliferative diseases in general that is now presently claimed.

Scope of Enablement Requirement

Claims 15-24 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the use of amonafide in conjunction with cisplatin, paclitaxel, vinblastine, etoposide, 5-fluorouracil, homoharringtonine, colchicine, curcumin and parthenolide for the treatment of fibrosarcoma, does not reasonably provide enablement for the use of any naphthalimide in conjunction with any antiproliferative agent for the treatment of any cellular proliferative disease. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with the claims.

In this regard, the application disclosure and claims have been compared per the factors

indicated in the decision *In re Wands*, 8 USPQ2d 1400 (Fed. Cir., 1988) as to undue experimentation. The factors include:

1) the nature of the invention;
2) the breadth of the claims;
3) the predictability or unpredictability of the art;
4) the amount of direction or guidance presented;
5) the presence or absence of working examples;
6) the quantity of experimentation necessary;
7) the state of the prior art; and,
8) the relative skill of those skilled in the art.

The relevant factors are addressed below on the basis of comparison of the disclosure, the claims and the state of the prior art in the assessment of undue experimentation.

Factors 1 and 2) The presently claimed invention is directed to a method for treating a host with a cellular proliferative disease comprising contacting the host with a naphthalimide comprising amonafide in conjunction with an antiproliferative agent comprising homoharringtonine, wherein each active compound is present in an amount sufficient to modulate said cellular proliferative disease (see present claims 15-24). The invention is also directed to a composition comprising amonafide and homoharringtonine (see present claim 25).

Factors 3 and 7) In particular, one skilled in the art could not practice the presently claimed subject matter without undue experimentation because the artisan would not accept on its face that the treatment of all solid tumors could be effectively achieved by the administration of the claimed combination of a naphthalimide (e.g., amonafide) and an antiproliferative agent (e.g., cisplatin, paclitaxel, vinblastine, etoposide, 5-fluorouracil, homoharringtonine, colchicine, curcumin and parthenolide). Based on the state of the art, as discussed below, the artisan would

have only accepted that the treatment of specific types of solid tumor could be achieved with particular combinations of naphthalimide and antiproliferative agent, rather than that such a combination of agents could have been used to treat any known solid tumor.

As set forth in *In re Marzocchi et al.*, 169 USPQ 367 (CCPA 1971):

"[A] [s]pecification disclosure which contains teaching of manner and process of making and using the invention in terms corresponding to the scope to those used in describing and defining subject matter sought to be patented must be taken as in compliance with the enabling requirement of first paragraph of 35 U.S.C. 112 *unless there is reason to doubt the objective truth of statements contained therein which must be relied on for enabling support*; assuming that sufficient reasons for such doubt exists, a rejection for failure to teach how to make and/or use will be proper on that basis, such a rejection can be overcome by suitable proofs indicating that teaching contained in the specification is truly enabling." (emphasis added).

The present claims circumscribe a method of treating all solid tumors. That is, in order to be enabled to practice the present invention, the skilled artisan would have to accept that by administering the presently claimed combination of active agents, all solid tumors known in the art could be treated. However, such a situation is sufficiently unusual that data would need to be shown in order to establish which specific types of solid tumor would have sensitivity to such a composition and how such tumors could be effectively treated through the administration of the claimed active agents. Because the specification fails to direct the skilled artisan as to which other tumors aside from fibrosarcoma are known to be sensitive to such a composition, and especially in consideration of the highly complex nature of tumors and cancer in general, the specification, which lacks an objective showing of which solid tumors other than fibrosarcoma

could be effectively treated using the claimed combination of active agents, is viewed as lacking an enabling disclosure of the same.

Here, the objective truth that solid tumors of any type may be treated is doubted because, while the state of the art of cancer treatment is well developed with regard to the *treatment* of *specific* cancer types (see Cecil's Textbook of Medicine at page 1060-1074), the state of the art with regard to treating cancer *in general* is grossly underdeveloped.

In this regard, Cecil's Textbook of Medicine (2000) is cited. In particular, there is no known anticancer agent or combination of anticancer agents that is effective against treating all cancer types, nor is there any known anticancer agent or combination of agents that is effective against inhibiting the growth of any type of cancer cell. The Cecil reference clearly shows that for the various known cancer types, there is not one specific chemotherapeutic agent or combination thereof that is effective at treating cancer or inhibiting the growth of cancer cells for each and every type of cancer (see Table 198-5 at page 1065; Tables 198-6 and 198-7 at page 1066; Table 198-8 at page 1068; and Table 198-9 at page 1071).

Given that there was not known any specific agent or combination of agents effective to treat all known types of cancer, one of ordinary skill in the art would not accept on its face Applicant's statement that such an objective could be achieved in any type of solid tumor using the presently claimed combination of agents. The artisan would have required sufficient direction as to which specific types of solid tumor could be effectively treated with the presently claimed combination of active agents and, further, how the artisan could determine what types of solid tumor would actually show sensitivity to the presently claimed composition without undue experimentation, such that the artisan would have been imbued with at least a reasonable

expectation of success in treating the tumor. Such success would not have been reasonably expected for all solid tumor types given the highly complex and variable nature of all cancers known in the art and that the treatment of all known solid tumor types would have been an outcome not reasonably expected by one of ordinary skill in the art. To the artisan, the concept of a single agent, or even a combination of agents, that is effective to treat all known types of solid tumor would have been unique and, thus, met with a great deal of skepticism.

Factor 4) Applicant has merely disclosed the genus of naphthalimides and antiproliferative agents and that by employing any combination of the two that one may achieve the therapeutic treatment of any cellular proliferative disease, including any solid tumor. However, based upon the discussion above under the heading "Written Description", Applicant has not adequately identified what other naphthalimides, other than amonafide, or what other antiproliferative agents, other than cisplatin, paclitaxel, vinblastine, etoposide, 5-fluorouracil, homoharringtonine, colchicine, curcumin and parthenolide, would actually have efficacy in achieving the presently claimed therapeutic objective of treating a cellular proliferative disease, other than fibrosarcoma. In other words, Applicant has failed to demonstrate that he was in possession of the whole genus of naphthalimide compounds; the whole genus of antiproliferative agents; or the use of any naphthalimide and any antiproliferative agent for the treatment of the entire genus of cellular proliferative diseases. The mere exemplification of one naphthalimide, nine antiproliferative agents and one cellular proliferative disease is not sufficient to claim the entire, vast genus of compounds or diseases without so much as even identifying the other compounds or diseases that fall within such a genus and why the skilled artisan would have reasonably expected the same activity using any other combination(s) of agents aside from those

expressly disclosed by the present specification. There is also a conspicuous lack of reasonably or scientifically sound reasoning as to why one of ordinary skill in the art would have extrapolated the results shown with amonafide in combination with cisplatin, paclitaxel, vinblastine, etoposide, 5-fluorouracil, homoharringtonine, colchicine, curcumin and parthenolide for the treatment of fibrosarcoma to be representative of the activity of any one naphthalimide in combination with any one antiproliferative for the treatment of any one cellular proliferative disease. Such disclosure, or lack thereof, clearly is not adequate direction or guidance as to how to practice the entirety of the presently claimed invention.

Factor 5) The specification fails to provide adequate guidance as to how one skilled in the art would accomplish the objective of achieving the treatment of any cellular proliferative disease using any known naphthalimide in combination with any known antiproliferative agent, since Applicant has not provided adequate written description to support the claim that he was actually in possession of the entire genus of naphthalimides, antiproliferative agents or cellular proliferative diseases. In addition, Applicant has also failed to provide sufficient support for the claim that the disclosed combination of agents may be used to effectively treat any known type of solid tumor.

The Examiner acknowledges that the Office does not require the presence of working examples to be present in the disclosure of the invention (see MPEP §2164.02). However, given the highly unpredictable state of the art and, furthermore, given that Applicant has failed to provide adequate guidance or direction as to how to practice the full scope of the presently claimed invention without undue experimentation, the Office would require appropriate disclosure, in the way of concrete examples or other scientifically sound reasoning, as to why the

data shown is a reasonably representative and objective showing such that it was commensurate in scope with and, thus, adequately enables, the present claims. Absent such evidence or reasoning, Applicant has failed to obviate the presumption of unpredictability in the art.

Factor 6) Applicant has failed to provide guidance as to which particular combination of naphthalimide and antiproliferative agent would be preferred for the treatment of any cellular proliferative disease other than fibrosarcoma in the present disclosure. The skilled artisan would expect the interaction of a particular combination of drugs in the treatment of a particular disease state to be very specific and highly unpredictable absent a clear understanding of the structural and biochemical basis for the use of each agent. The instant specification sets forth no such understanding or any criteria for extrapolating beyond the combination of amonafide and cisplatin, paclitaxel, vinblastine, etoposide, 5-fluorouracil, homoharringtonine, colchicine, curcumin and parthenolide for the treatment of fibrosarcoma. Even for the combinations set forth, no direction is provided to use any other naphthalimide other than amonafide; any other antiproliferative agent other than cisplatin, paclitaxel, vinblastine, etoposide, 5-fluorouracil, homoharringtonine, colchicine, curcumin and parthenolide; or any other condition beyond fibrosarcoma. Absent any sound scientific reasoning as to why the results shown with the disclosed combinations would have been reasonable predictive of the same or substantially similar success using the breadth of agents presently claimed, one skilled in the art would have no other recourse but undue experimentation to undertake extensive testing to determine what combination of agents would actually demonstrate efficacy in the treatment of which particular cellular proliferative disease(s).

Furthermore, it is noted that the burden of enabling the treatment of all types of solid tumor is much greater than that of enabling the treatment of a specific, discrete group of solid tumor known to, or with a reasonable basis for concluding that they would, be responsive to such a treatment. Since the present specification would not enable the skilled artisan to treat any type of solid tumor known in the art, a clear burden of undue experimentation would be placed upon the skilled artisan in order to practice the full scope of the presently claimed invention.

Factor 8) In view of the discussion of each of the preceding seven factors, the level of skill in the art is high and is at least that of a medical doctor with several years of experience in the art.

As the cited art and discussion of the above factors establish, practicing the claimed method in the manner disclosed by Applicant would not imbue the skilled artisan with a reasonable expectation that the use of any naphthalimide in combination with any antiproliferative agent would have efficacy in the treatment of any cellular proliferative disease. In order to actually achieve such a result, it is clear from the discussion above that the skilled artisan could not rely upon Applicant's disclosure as required by 35 U.S.C. 112, first paragraph, and would have no alternative recourse but the impermissible burden of undue experimentation in order to practice this embodiment of the claimed invention.

Claim Rejections - 35 USC § 112, Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

I Claims 15-24 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention.

A broad range or limitation together with a narrow range or limitation that falls within the broad range or limitation (in the same claim) is considered indefinite, since the resulting claim does not clearly set forth the metes and bounds of the patent protection desired. See MPEP §2173.05(c). Note the explanation given by the Board of Patent Appeals and Interferences in *Ex parte Wu*, 10 USPQ2d 2031, 2033 (Bd. Pat. App. & Inter. 1989), as to where broad language is followed by "such as" and then narrow language. The Board stated that this can render a claim indefinite by raising a question or doubt as to whether the feature introduced by such language is (a) merely exemplary of the remainder of the claim, and therefore not required, or (b) a required feature of the claims. Note also, for example, the decisions of *Ex parte Steigewald*, 131 USPQ 74 (Bd. App. 1961); *Ex parte Hall*, 83 USPQ 38 (Bd. App. 1948); and *Ex parte Hasche*, 86 USPQ 481 (Bd. App. 1949).

In the present instance, claim 15 recites the broad limitation "contacting said host with a naphthalimide", and then goes on to state "comprising an amonafide", a narrower statement of the limitation. In addition, claim 15 also recites the broad limitation "with an antiproliferative agent" and then goes on to state "comprising homoharringtonine", a narrow statement of the limitation. Such recitations renders the claim indefinite because it is unclear as to whether Applicant intends to claim the use of any naphthalimide compound in combination with any antiproliferative agent for the treatment of any host with a cellular proliferative disease, or if Applicant intends to claim the use of the specific combination of amonafide and

homoharringtonine for the treatment of any host with a cellular proliferative disease. As a result, the boundaries of the claim cannot be identified.

In addition, the very recitation of "naphthalimide comprising" or "antiproliferative agent comprising" fails to clearly delineate whether amonafide and homoharringtonine are required to be present as components of the composition of the naphthalimide and the antiproliferative agent to be administered, or whether such agents are merely an exemplary combination that may be employed in the presently claimed method.

For these reasons, claims 15-24 fail to meet the tenor and express requirement of 35 U.S.C. 112, second paragraph, and are, thus, properly rejected.

For the purposes of examination and the application of prior art, the claims will be interpreted to read upon the use of any naphthalimide compound in combination with any antiproliferative agent for the treatment of a host with a cellular proliferative disease.

II Claims 15-21 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention.

The MPEP sets forth the following at §2173:

> "The primary purpose of this requirement of definiteness of claim language is to ensure that the scope of the claims is clear so the public is informed of the boundaries of what constitutes infringement of the patent. A secondary purpose is to provide a clear measure of what applicants regard as the invention so that it can be determined whether the claimed invention meets all the criteria for patentability and whether the specification meets the criteria of 35 U.S.C. 112, first paragraph with respect to the claimed invention." (See MPEP §2173).

The term "modulate" in the expressions "each in an amount sufficient to modulate said

cellular proliferative disease" (see present claim 15) or "wherein the modulation of said disease with said naphthalimide and said antiproliferative agent is greater than that for said naphthalimide or said antiproliferative agent alone" (see present claim 19) is a relative term that renders the claim indefinite. The expression "modulate" is not defined by the claims to properly delineate the effect that is intended from administration of a combination of a naphthalimide and an antiproliferative agent.

Applicant discloses at page 3, lines 7-15 of the present specification:

> "The agents are provided in amounts sufficient to modulate a cellular proliferative disease. In one embodiment, modulation of a cellular proliferative disease comprises a reduction in tumor growth. In another embodiment, modulation of a disease comprises inhibition of tumor growth. In another embodiment, modulation of a cellular proliferative disease comprises an increase in tumor volume quadrupling time (described below). In another embodiment, modulation of a cellular proliferative disease comprises a chemopotentiator effect. In another embodiment, modulation of a disease comprises a chemosensitizing effect. In other embodiments, modulation of a disease comprises cytostasis. In still other embodiments, modulation of a disease comprises a cytotoxic effect."

In particular, it is noted that the word "modulate" encompasses a variety of effects, which Applicant has failed to define adequately in the present claims or disclosure in order to convey to one of ordinary skill in the art the intended scope of the invention, namely, whether the term encompasses each one of the above-mentioned effects, at least two or more, etc. Furthermore, absent any standard for ascertaining the requisite degree of "modulation", the use of such a term would invite subjective interpretations of whether or not a particular change in function or effect is encompassed by or excluded from the present claims. Thus, it is the Examiner's position that the public would not be informed of the boundaries of what constitutes infringement of the present claims.

For these reasons, the claims fail to meet the tenor and express requirements of 35 U.S.C.

§112, second paragraph and are, therefore, properly rejected.

Claim Rejection - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 15-25 are rejected under 35 U.S.C. 103(a) as being unpatentable over Scheithauer et al. ("Phase II Study of Amonafide in Advanced Breast Cancer", *Breast Cancer Research and Therapeutics*, 20:63-67, 1991) in view of Jiang et al. ("Comparative *In Vitro* Antitumor Activity of Homoharringtonine and Harringtonine Against Clonogenic Human Tumor Cells", *Investigational New Drugs*, 1:21-25, 1983).

Scheithauer et al. teaches the treatment of patients with advanced breast cancer (i.e., a host with a cellular proliferative disease as required by present claim 15 and a solid tumor as required by present claim 21) using amonafide (see present claim 15) at a dose of 800 mg/m^2 intravenously over 3 hours repeated every 4 weeks (i.e., in an amount sufficient to modulate said cellular proliferative disease as required by present claim 15; see abstract and paragraph bridging columns 1 and 2 at page 64). Scheithauer et al. teaches, "In summary, our results suggest that amonafide in an active agent in the treatment of patients with advanced breast cancer. The drug should therefore be considered for further evaluation and incorporation in combination chemotherapy." (see present claim 15 and the last paragraph of column 1 at page 67).

The differences between the Scheithauer et al. reference and the presently claimed subject matter lie in that the reference fails to teach:

(i) the concomitant use of homoharringtonine with amonafide or a composition comprising both amonafide and homoharringtonine, wherein the effect of such a combination on the cellular proliferative disease is greater than that of each individual agent alone (see present claim 15, 19 and 25) and the subsequent reduction in tumor growth (see present claim 22), inhibition of tumor growth (see present claim 23) or increase in tumor volume quadrupling time (see present claim 24); or

(ii) the presently claimed dosing regimen (i.e., naphthalimide administered before, during or after the antiproliferative agent; see present claims 16-18).

However, the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains because:

(i) Jiang et al. provides teachings that the alkaloid compound homoharringtonine, derived from the Chinese evergreen tree *Cephalotaxus harringtonia*, was known in the art to demonstrate significant antitumor activity in solid tumors, including ovarian, endometrial and breast cancer, as well as sarcoma. In particular, Jiang et al. teaches "In the continuous exposure studies, homoharringtonine provide to be more potent that harringtonine. Significant antitumor activity of homoharringtonine was noted in sarcoma and breast cancer as well as in ovarian and endometrial carcinoma." (see Summary at page 21). One of ordinary skill in the art would have been motivated to use amonafide in conjunction with homoharringtonine for the treatment of

breast cancer (i.e., a cellular proliferative disorder as required by claim 15 and also a solid tumor as required by claims 20-21) since each was known separately in the art to have significant therapeutic activity in the treatment of breast tumors. Motivation to administer both compounds flows logically from this shared efficacy and the demonstration in the prior art that each had been previously administered for the same therapeutic endpoint. Such a common function of each of the compounds would have raised the reasonable expectation of success that the combination of both amonafide and homoharringtonine would have achieved, at minimum, a potentiated antitumor effect, such that the effect of the agents when combined would have been greater than the effect achieved by either single agent alone. In the absence of evidence to the contrary, it is generally *prima facie* obvious to use in combination two or more agents that have previously been used separately for the same purpose. Please also reference *In re Kerkhoven*, 205 USPQ 1069 (CCPA). In addition, it is noted that Scheithauer et al. expressly directs the skilled artisan to consider amonafide for use in combination chemotherapeutic regimens, which also raises the reasonable expectation that amonafide would have been amenable to combination with other antitumor agents, such as homoharringtonine.

Similar reasoning applies to the combination of amonafide and homoharringtonine into a single pharmaceutical composition as required by present claim 25. Once again, motivation to administer the two compounds in a single formulation would have been *prima facie* obvious to one of ordinary skill in the art, since each was known to exhibit efficacy in the treatment of breast cancer and would have been reasonably expected to achieve a greater antitumor effect when combined than when given individually, absent factual evidence to the contrary.

Furthermore, it is noted that the antitumor activity of each of amonafide or homoharringtonine would have necessarily had an effect on reducing or inhibiting the growth of the tumor such that a positive response to the therapeutic regimen would have been observed. Such a slower rate of tumor growth would have also necessarily resulted in an increase in tumor volume quadrupling time. Thus, while Applicant recites limitations wherein the modulation of the proliferative disease comprises both a reduction or inhibition of tumor growth as well as an increase in the tumor volume quadrupling time, such results are not effects that would not have been reasonably expected by the skilled artisan and, therefore, are not considered a patentable distinction over what was already known in the prior art.

(ii) The determination of the optimum dosing regimen to treat a solid tumor (e.g., breast cancer) with the presently claimed active agents would have been a matter well within the purview of one of ordinary skill in the art. Such a determination would have been made in accordance with a variety of factors, such as the dosage amount(s) to be administered based on the age, weight, sex, diet and medical condition of the patient, severity of the disease, the route of administration, pharmacological considerations, such as the activity, efficacy, pharmacokinetics and toxicology profiles of the particular compound employed, whether a drug delivery system is utilized and adverse reactions and patient tolerability to the regimen. Thus, the sequential or simultaneous order of administration would have actually been employed would have varied in accordance with these factors and, in the absence of evidence to the contrary, is not seen to be inconsistent with the order of administration that would have been readily and easily determined by the skilled artisan by routine experimentation.

Double Patenting

Obviousness-Type Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 15-24 are rejected under the judicially created doctrine of obviousness-type double patenting over the method claims of U.S. Patent No. 6,630,173 and are provisionally rejected under the judicially created doctrine of obviousness-type double patenting over the method claims of U.S. Patent Application Nos. 11/067,074; 10/976,961; and 10/625,866.

Claim 25 is provisionally rejected under the judicially created doctrine of obviousness-type double patenting over the claims 42-44 of U.S. Patent Application No. 10/976,961.

This is a provisional double patenting rejection over U.S. Patent Application Nos. 11/067,074; 10/976,961; and 10/625,866; since the conflicting claims of such applications have not yet been patented.

This is a non-provisional double patenting rejection over U.S. Patent No. 6,630,176, since

the conflicting claims have been issued as a United States Patent.

Due to the number of applicable different patents and patent applications, a detailed analysis of why the presently claimed subject matter would have been an obvious variation over each one of the applicable claims in the various patent applications is not presented, but the rejection set forth below is representative of and applicable to all of the above-cited or patent applications, but for the differences in claim numbering.

Claims 15-24 are rejected under the judicially created doctrine of obviousness-type double patenting over claims 1-8 of U.S. Patent No. 6,630,173.

For the following reasons, the presently claimed subject matter would have been obvious not only over such claims, but over each of the applicable claims of the remaining U.S. Patent Applications cited above.

An obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but an examined application claim is not patentably distinct from the reference claims because the examined claims is either anticipated by, or would have been obvious over, the reference claims.

Although the conflicting claims are not identical, the claims of the U.S. Patent and those of the present patent application are not considered patentably distinct from each other because the patented claims anticipate the copending claims.

In particular, it is noted that the patented claims clearly provide for the treatment of a host with a cellular proliferative disease, such as a solid tumor, comprising the administration of a naphthalimide comprising amonafide in conjunction with an antiproliferative agent comprising cisplatin in amounts sufficient to modulate the disease and wherein the modulation achieved by

both agents in combination is greater than that achieved by either agent alone. The patented claims clearly provide for the administration of the naphthalimide before, during or after the antiproliferative agent and further state that the modulation comprises the reduction or inhibition of tumor growth and the increase in tumor volume quadrupling time.

The present claims are drawn to a same therapeutic objective, but it is noted that the language of the claim does not make clear whether it is limited to the genus of antiproliferative agents or, specifically, homoharringtonine. As a result, the present claims read on the use of any antiproliferative agent. In light of this fact, the very recitation of the species of cisplatin in the patented claims renders the genus of "antiproliferative agents" of the present claims anticipated. See MPEP §2131.02 for a discussion of genus-species situations.

Accordingly, rejection of claims 15-24 of the present application is deemed proper over claims 1-8 of U.S. Patent No. 6,630,173 and over the method and/or composition claims of each of the other cited U.S. Patent Applications as claiming obvious and unpatentable variants thereof.

Conclusion

The prior art made of record but not relied upon is considered pertinent to Applicant's disclosure. Please reference U.S. Patent No. 5,183,821 to Brana et al. ("Method for Treating Leukemias Using N-(2-dimethylaminoethyl)-3-amino-1,8-naphthalimide for Treating Leukemias and Solid Tumors"), U.S. Patent Application Publication No. 2001/0049349 to Chinery et al. ("Antioxidant Enhancement of Therapy for Hyperproliferative Conditions"), and Witte et al. ("A Phase II Trial of Amonafide, Caracemide, and Homoharringtonine in the Treatment of Patients with Advanced Renal Cell Cancer").

Rejection of claims 15-25 is deemed proper.

No claims of the present application are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Leslie A. Royds whose telephone number is (571)-272-6096. The examiner can normally be reached on Monday-Friday (8:30 AM-5:00 PM).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low can be reached on (571)-272-0951. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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March 16, 2006

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